Encapsulating Peritoneal Sclerosis: Clinical Significance and Implications

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\textbf{Key Words}
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\textbf{Abstract}
Encapsulating peritoneal sclerosis (EPS) is a rare but serious complication of peritoneal dialysis (PD). This review discusses the current understanding of the aetiology and pathogenesis of EPS, highlighting histological features which differentiate it from simple sclerosis of the peritoneal membrane which develops with time on PD. Diagnostic criteria are presented, including the role of imaging techniques. To date there are no randomised controlled trials to guide therapy; however, surgical techniques are an important treatment option. Collaborative research will be essential if this serious problem facing PD is to be solved.

\textbf{Introduction}
Encapsulating peritoneal sclerosis (EPS) is a rare but potentially devastating complication of peritoneal dialysis (PD). Diagnosis comprises the fulfilment of two key criteria: firstly, symptoms that might indicate an obstructive ileus, which may range from mild symptoms such as anorexia to marked weight loss and bowel obstruction \cite{1}, and secondly the demonstration, either at laparotomy or from imaging techniques, that this ileus is due to peritoneal membrane thickening resulting in encapsulation and coconing of the bowel. However, it is recognised that onset is often insidious, presenting with non-specific features of inflammation, weight loss and abdominal discomfort, whereas the full-blown form can cause failure of the gastrointestinal tract and death. Its sporadic nature, the difficulty in early diagnosis, as well as the lack of suitable animal models, means that at present the understanding of risk factors of EPS is incomplete and evidence-based therapies are lacking. In some patients, EPS seems to be a self-limiting condition that can be managed with appropriate nutritional support, whereas in others the progression is rapid with the development of obstructive features, and in these cases there is growing evidence that timely surgical intervention can be successful.

\textbf{Aetiology}
The incidence of EPS varies between reports partly as a consequence of difficulties with diagnostic definition requiring sufficient sensitivity to include all cases while...
maintaining specificity. In a prospective study from Japan, the incidence rates and mortality rates increased with time on PD ranging from 0% at 3 years to 5.8% at 10 years to 17.2% with 100% mortality in patients on PD for over 15 years [1]. EPS is not exclusive to PD and has been associated with a range of conditions, including systemic autoimmune disease, diseases of the gastrointestinal tract, peritoneal and intra-abdominal malignancies, exposure to talc or particulate matter or the use of intraperitoneal disinfectant for peritoneal lavage and β-blocker administration [1]. Although peritoneal sclerosis can be induced in animal models by infusing a range of sclerosant agents into the peritoneal cavity [2] and more recently the introduction of profibrotic agents delivered to the peritoneum via adenoviruses [3], it has been difficult in animals to adequately mimic the human condition where prolonged dialysis in the context of uraemia and inflammation contributes to the formation of the abdominal cocoon. In PD patients, clinical associations have been identified with acetate buffer [4], chlorhexi-
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surgery exhibit local fibrinolytic abnormalities. Plasmin has a central role not only in fibrin degeneration, but also in the breakdown of extracellular matrix, activation of metalloproteinases, and activation of uPlasminogen activator – and thus may be central to the process [14]. An overexpression of TGF-β1 is associated with adhesion formation, possibly through a mechanism involving local regulation of plasminogen activator inhibitor type 1 [15].

The molecular mechanisms involved in the development of EPS are complex and include dysregulation of growth factors combined with subclinical bowel ischaemia resulting in transmigration of gut organisms across the bowel wall.

In parallel with fibrosis, the peritoneum shows a progressive increase in capillary number (angiogenesis) and vasculopathy, resulting in increased solute transport across the peritoneal membrane and ultrafiltration failure. Glucose and glucose degradation products contained in the dialysate may have a role in peritoneal deterioration and stimulate transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) production by mesothelial cells. TGF-β is a potent profibrotic factor and induces epithelial-mesenchymal transition of the mesothelial cells. Local production of VEGF during PD plays a central role leading to peritoneal neoangiogenesis and PD functional decline [16].

**Diagnosis**

Clinically, the diagnosis of EPS is based on the finding of abnormalities in gastrointestinal function [1]. Symptoms include early satiety, anorexia, nausea, vomiting, constipation, diarrhoea, weight loss, abdominal fullness and pain [17]. Signs of inflammation may be pyrexia, raised CRP, anaemia, bloody dialysate, and ascites. Abdominal masses and pain may indicate peritoneal adhesions and/or coocooning, and there may be features of acute or subacute intestinal obstruction. Loss of peritoneal ultrafiltration capacity is common and a rapid increase in small solute peritoneal transport as defined in the peritoneal equilibration test has also been described. The differential diagnosis includes TB peritonitis, peritoneal mesothelioma, carcinomatosis or posttransplant small bowel lymphoma, and it is important to obtain histology where there is doubt. Japanese investigators [17] have subcategorised EPS into four stages: pre-EPS; an inflammatory stage; an encapsulating stage, and finally a stage of bowel obstruction. Classifying the diagnosis according to progressive stages has the potential for therapeutic strategies to be appropriately targeted to the phases of development.

Current imaging techniques are insufficiently sensitive to detect the early stages of EPS. Screening with CT is of limited value since up to 50% of patients with established EPS have had a normal abdominal CT within 2 years prior to diagnosis [18], whereas peritoneal abnormalities are present in approximately 7% of patients on long-term PD who do not develop EPS, with thickening and enhancement being most prevalent [19]. CT scanning is the investigation of choice in patients with established EPS [19, 20] (table 1; fig. 2) and is useful for monitoring disease progression. However, interpretation can be difficult and scans should be read by an experienced radiologist familiar with the condition. Findings include peritoneal enhancement after intravenous contrast, with peritoneal thickening,
alcoholic bowel joins with an encapsulated segment, separa-
tion and is most easily assessed if the bowel lies within a
loculated fluid collection (cocoon). Other CT features
include bowel wall thickening and dilatation which may
be associated with obstruction. Ultrasound findings in-
clude increased peristalsis, bowel tethering, ascites and
visualisation of a previsceral membrane [21]. The main
feature on barium studies is delayed transit [22], but
there may also be an abrupt change in calibre where nor-
mal bowel joins with an encapsulated segment, separa-
tion of rigid bowel loops and disordered peristalsis [23].
MRI is not particularly helpful since it is not good at as-
sessing peritoneal calcification and there are concerns
about nephrogenic systemic fibrosis from contrast stud-
ies in dialysis patients.

Management

There are no randomised controlled trials to inform
the management of patients with EPS and the level of
evidence is weak. Reported therapy includes the use of
immunosuppressant agents, predominantly corticoste-
roids, the antifibrotic agent tamoxifen, nutritional sup-
port and surgery to remove the fibrotic material (enter-
olysis/adhesiolysis) [24]. In a registry report from Japan,
out of a total of 1,958 patients treated with PD, 48 devel-
oped EPS in whom the recovery ratio with total paren-
teral nutrition, corticosteroids and surgical treatment
were 0, 38.5, and 58.3%, respectively [25]. Nutritional as-
sessment and support is critical to patient outcome, and
patients may require enteral or parenteral support, with
preoperative optimisation of patients undergoing enter-
olysis being essential [26]. Surgery has an important role
in the management of established EPS and is probably
currently the only definitive therapeutic measure. Kaw-
nishi et al. [27] reported that enterolysis was successful in
81 of 86 cases with, however, a 23% recurrence rate. In the
UK, the Manchester group has carried out peritonectomy
and enterolysis in 62 cases of established EPS since Janu-
ary 2000. 43 (69%) patients are currently alive and well.
Mortality in this series has been mainly in the advanced
cases operated on as surgical emergencies [publication in
preparation].

There is an urgent need to precisely define the role
and timing of surgery in EPS. Currently described poor
outcomes of surgery in individual cases or small case se-
ries are a consequence of delayed surgical intervention,
often as an emergency in nutritionally depleted, septic
and obstructed renal failure patients. It highlights the
need to have well-defined criteria for diagnosis, length
of medical treatment with timely recognition of failure
of medical treatment and referral for surgery before the
patient’s condition deteriorates. Furthermore, it is criti-
cal that the patient’s condition is optimised prior to sur-
gery. Good surgical outcomes require a multidisciplinary
team, with surgeons experienced in peritonectomy and
enterolysis, along with intensive perioperative haemodi-
alysis, parenteral nutrition, physiotherapy and critical
care. Operative management entails stripping of the
thickened parietal and visceral peritoneal membrane
(peritonectomy) and release of the small bowel obstruc-
tion (enterolysis) and can last several hours, be demand-
ing and require the utmost care to avoid an inadvertent
enterotomy, which could be a fatal complication. Provid-
ing surgical care for EPS patients has significant implica-
tions for service development and training to ensure suf-
cient expertise in this area. In the UK, the National
Specialist Commissioning Group has designated Man-
chester and Cambridge as national referral centres for
the surgical treatment of established cases of EPS from
April 2009. With centralising and increasing experience
at these two centres already undertaking peritonectomy
and enterolysis, it is envisaged that overall outcomes can
be further improved while facilitating further research
into EPS.
Prevention

An understanding of the aetiology of EPS should lead to a reduction in the risk for patients on PD [28]. Thus, low glucose exposure, preserved residual renal function, little or no peritoneal infection, and low small solute transport status may confer a lower individual risk. PD management should focus on minimising glucose exposure and peritonitis rates. Japanese data has suggested a dramatic increase in the incidence of EPS after 8 years on therapy and recommendations have been made to preemptively discontinue PD at that stage [24]. The dilemma is that for some patients, discontinuation is a risk factor for triggering EPS.

References


The Way Forward – The Need for an International Registry

It is clear that there is much to do to improve our understanding of EPS, and this will require a collaborative research approach. In the UK, an EPS registry and DNA bank have been established in the context of a nationwide PD research network with support from the International Society of Peritoneal Dialysis (ISPD) and the Kenyon Gilson Fund [29]. Objectives include the development of a risk-based approach to clinical decision making by collecting detailed risk factor data in combination with genetic analysis and additional biomarkers and correlating these with outcomes. Candidate genes include genes of fibrosis (TGF), angiogenesis (VEGF, RAGE), and inflammation (TNF, IL-6). Such a research network will also permit better understanding of the effects of treatment and indeed provide a platform for clinical trials and will necessarily collaborate internationally. It is hoped that through such an initiative, EPS will cease to haunt PD in the foreseeable future.
This review addresses an important, serious and often underestimated complication of long-term CAPD, namely encapsulating peritoneal sclerosis (EPS). Augustine and colleagues have highlighted in their review the clinical, pathological as well as radiological features of EPS. They also review the pathophysiology of the peritoneal fibrosis which shares common pathways with other forms of fibrosis, including a putative important role attributed to transforming growth factor-β1. The authors examine critically the limited available data on surgical and medical interventions. They draw some conclusions and a list of recommendations and guidelines for early detection and management. They also draw attention to the recently formed UK EPS registry and DNA bank to foster clinical collaboration and research in the field. This registry is supported by the International Society of Peritoneal Dialysis (ISPD) and the Kenyon Gilson Fund. Readers with an interest in the field should contact Dr. Martin Wilkie at the Sheffield Kidney Institute, Sheffield, UK (martin.wilkie@sth.nhs.uk).